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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/849,498	YANG ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8-16,44 and 49-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 8-16, 44 and 49-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendments to the Claims, filed 18 November 2009, have been received and entered. Claims 2, 6-7, 17-43 and 45-48 are cancelled. Claims 1, 3-5, 8-16, 44 and 49-54 are pending and under examination in this action.

Response to Amendment

All rejections not repeated are withdrawn herein.

The rejection of Claims 49 and 54 under 35 U.S.C. 102(a) and 102(e) as being anticipated by Lollo et al (USPGPub 2003/0134420A1) is withdrawn based on the amendment to the claims "wherein the backbone comprises a graft co-polymer".

Claim Rejections - 35 USC § 102-maintained in part

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-5, 8-16, 44 and 50-53 STAND rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Lollo et al, (USPGPub 2003/0134420A1, filed 2 August 2002, published 17 July 2003, see whole document, of record) for reasons of record and below.

Applicants arguments have been fully considered but are not found persuasive (addressed below).

Claim interpretation: Claims must be given their broadest reasonable interpretation in light of the instant specification during examination. Accordingly, the terms such as "associated" must be given a very broad interpretation regarding the claim language in part because Applicant provides a broad description in the specification for how molecules may be associated and dissociated with one another for the claimed invention. Applicant recites: "A first molecule may be "associated" with a second molecule, under set conditions, if the two molecules move together as a unit under these conditions. For example, the two molecules may be immobilized with respect to each other. The two molecules may be covalently or ionically bonded, may be joined by Van der Waal's forces or magnetic forces or one molecule may be physically contained or trapped by the second molecule or a collection of second molecules" [instant specification ¶ 0048]. Applicant further recites: "A first molecule may be "disassociated" from a second molecule or article with which it is associated. Disassociated means that the first molecule can move independently of the second molecule. The first molecule can also be disassociated from a second molecule or from an article if the second molecule or article degrades or is broken down so that it is no longer linked to the first molecule" [instant specification ¶ 0049].

Claims are drawn to an article for delivering a drug and a nucleic acid, the article comprising: a nanoparticle forming a micelle, wherein the nanoparticle comprises a polymer having a backbone comprising a polyester; a nucleic acid associated with an exterior of the micelle; and a drug associated with an interior of the micelle (claim 1). Applicants further claim

wherein the nucleic acid is DNA (claim 4), and wherein the article is in a composition with a pharmaceutically acceptable carrier (claim 10). Applicants also claim wherein the nanoparticle is capable of passing through a cell membrane, is stable at a concentration of greater than 5 mg/L (claims 3 and 8). Claim 11 is drawn to an article as in Claim 1 wherein the backbone comprises tertiary amines). Claim 15 further specifies within Claim 11 that at least a portion of the tertiary amines are quaternized and bound to a hydrophobic side chain. Claims 52 and 53 are drawn to an article as in Claim 1 wherein the drug is not covalently or ionically bound to the nanoparticle (Claim 52) and is physically contained by the nanoparticle (Claim 53).

Lollo et al teach wherein the article forms a micelle and further teach wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle (claims 1 and 44). For example, Lollo et al recite "the invention provides novel molecular complexes, referred to as "polyplexes" containing an anionic compound, such as a nucleic acid, associated with one or, more typically, multiple co-polymer domains, including a cationic domain, a transitional domain, and/or a surface domain (¶ 0005, lines 1-2).

> As shown in FIG. 1, polyplexes of the present invention are made up of multiple co-polymer domains. These domains are organized by the type of functional groups present on the co-polymer making up the domain. Typically, **the center domain** (Zone I of FIG. 1) contains the anionic agent. Examples of anionic agents include nucleic acids, **negatively charged drugs** and other small molecules capable of being delivered via a polyplex through a cellular boundary or lipid membrane. The cationic domain (Zone II of FIG. 1) is designed to interact, e.g., electrostatically, with the anionic domain/agent. Generally, the cationic domain is comprised of one or more cationic backbone moieties of copolymers, which are described in greater detail below. The transitional domain (Zone III of FIG. 1) links the cationic domain with the surface domain, typically via linear or branched co-polymers. The transitional domain may be hydrophobic in nature

and may be comprised, at least in part, of hydrophobic moieties of copolymers. When the transitional domain is comprised at least in part of hydrophobic moieties, it is generally referred to as the "hydrophobic domain." Finally, the surface domain (Zone IV of FIG. 1) defines the polyplex surface by way of, for example, branching elements which allow the introduction of multiple molecules or other polymers on the polyplex surface. Such moieties modify the surface properties of the polyplex so as to enhance overall delivery of the anionic agent. The surface domain may be comprised, at least in part, of hydrophilic moieties of copolymers, as well as other ligands and other surface moieties which allow the polyplex to perform its intended function [0032].

In addition, applicants claim the article in claim 1 wherein the drug is a cancer drug and wherein the article is in a composition with a pharmaceutically acceptable carrier (claims 5 and 10). Applicants also claim a kit comprising: a container including an amphoteric polymeric nanoparticle forming a micelle, wherein the polymeric nanoparticle comprises a polymer having a backbone comprising a polyester; a nucleic acid associated with an exterior of the micelle, a drug associated with an interior of the micelle; and instructions for administering the nanoparticle to a subject (claim 44).

Lollo et al teach a micelle complex comprised of amphoteric nanoparticles having a hydrophilic portion associating with DNA and/or cancer drugs and a hydrophobic portion capable of associating with cancer drugs and capable of passing through a cell membrane and capable of being directed to specific membranes by receptor-mediated targeting. In addition, Lollo et al contemplate a multidomain complex which can accommodate nucleic acids either on the interior or exterior and can accommodate drugs either on the interior or exterior (claims 50-52). For example, Lollo et al recite: “Typically, the center domain (Zone I of FIG. 1) contains the anionic agent. Examples of anionic agents include nucleic acids, negatively charged drugs

and other small molecules capable of being delivered via a polyplex through a cellular boundary or lipid membrane" (¶ 0032, lines 2-4 and especially ¶ 0031-0038).

Furthermore, Lollo et al anticipate using their invention to treat a subject and although they do not explicitly recite "instructions", it would be inherent that any treatment plan for treating a human subject would inherently require instructions. For example, Lollo et al recite "A method for treating a subject comprising administering to said subject an effective amount of a penetration enhancer and a polyplex comprising a nucleic acid, a cationic backbone moiety, a hydrophobic moiety, and a hydrophilic moiety, such that said subject is treated" (e.g. see Lollo et al claims 58, 59 and 68). Lollo et al anticipate using the complex to deliver genes and drugs *in vivo* and thus anticipate claims 10 and 44.

Furthermore Lollo et al teach wherein the article forms a micelle and further teaches wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle (claims 1 and 44). For example, Lollo et al teaches partially hydrophobic conjugates also may be used since they possess moieties that preserve sufficient water solubility (since purely hydrophobic molecules are water insoluble). These conjugates can be made up of two different types of grafts, hydrophilic moieties to maintain adequate water solubility (`A`), and hydrophobic moieties (`B`) to introduce a domain with binding and micelle formation properties. In one embodiment, the polymer is designed by grafting two or more of these elements onto a cationic backbone moiety (e.g., a cationic polymer, `C`) (claims 50-51). A suitable grafting element, or hydrophilic moiety for this approach is PEG, which promotes solubility and steric shielding. Another suitable grafting element is any hydrophobic moiety, as described above, which may form domains with binding capabilities. These two or more types of

grafting elements can then be randomly distributed along a cationic backbone moiety during the grafting step (¶ 0067, lines 1-6).

In addition, Lollo et al teaches an article as in claim 1 wherein the nanoparticle is stable at a concentration of greater than 5 mg/L because Lollo et al recites "polyplex concentration are reported by DNA content and were 10 ug/ml" which reads on the instant claim 8.

Furthermore, Lollo et al teach an article as in claim 1 wherein the nanoparticle comprises a graft co-polymer having a backbone including tertiary amines, at least a portion of the tertiary amines quaternized and bound to a hydrophobic side chain (claim 11), and further teaches wherein the hydrophobic side chain comprises cholesterol (claims 12 and 54). For example, Lollo et al teaches FIG. 11 shows the structure of grafted polymers with two hydrophobic domains per PEG chain. FIG. 11a shows a hydrophobic domain between the cationic domain and the surface domain. FIG. 11b shows a hydrophobic domain positioned at the terminus of a surface (e.g., hydrophilic) domain, and between the surface (e.g., hydrophilic) and cationic domains (¶ 0023, lines 1-3) (claims 50-53).

The applicants response (see REMARKS, 11/18/2009) is to traverse the rejection. The applicant argues that one of ordinary skill in the art would understand that "a polymer having a backbone comprising a polyester" means that polyester is part of the backbone and that the term "backbone" would not include side-chains and/or branches but refers to the portion of the polymer to which side-chains and/or branches are attached. The applicant argues that Lollo does not disclose the use of a polymer having a backbone comprising a polyester.

The applicants arguments have been fully considered but are not persuasive for reasons of record and presented herein. Specifically, as stated above, claims must be given their broadest

reasonable interpretation in light of the instant specification and therefore the phrase "a polymer having a backbone comprising a polyester" does not necessarily require a polyester backbone but rather a backbone comprising a polyester. For example, Applicants recite: "In one embodiment, the core shell nanoparticle may be made from a polymeric compound. The polymeric compound may include a portion capable of associating a nucleic acid and a second portion capable of associating a drug. The polymeric compound may be a branched polymeric compound and the branches may be grafted onto a backbone (instant specification, PgPub ¶ 0068). Therefore, the polyester component may be a side-chain or branch or otherwise associated component to any backbone molecule.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 8-16, 44 and 49-54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lollo et al (see above, of record), as applied to the claims above, in view of Pistel et al in "Brush-like branched biodegradable polyesters, part III: Protein release from microsheres of poly(vinyl alcohol)-graft-poly(D,L-lactic-co-glycolic acid)" (Journal of Controlled Release; 2001, Vol. 73:pages 7-20) for reasons of record and herein.

The applicants response is to traverse the rejection. The applicant argues that even if one were to combine the references of Lollo and Pistel, "one would not produce the articles taught in claims 1 and 44". Applicant submits that Pistel does not teach the use of backbones comprising a polyester but rather teaches the grafting of PLGA onto water-soluble PVAL backbones. The applicant argues that as polyvinyl alcohol does not comprise ester groups, the polyvinyl alcohol backbones do not comprise a polyester.

The applicants arguments have been fully considered but are unpersuasive. Contrary to the applicants assertions, Pistel et recite "brush-like branched polyesters, obtained by grafting poly(lactic-co-glycolic acid), PLGA, onto water-soluble poly(vinyl alcohol) (PVAL) backbones, were investigated regarding their utility for microencapsulation of proteins (e.g. abstract). Thus the rejection is maintained and repeated below.

As stated above, the claims may be interpreted broadly to be taught by Lollo et al for the reasons provided above. However, in an alternative interpretation of the amended claims, as argued by Applicant in REMARKS, Lollo et al does not explicitly teach a polyester backbone.

Pistel et al teach articles for delivering a drug comprising a nanoparticle forming a micelle, wherein the nanoparticle comprises a polymer having a backbone comprising a polyester. Pistel et al teach microencapsulation of hydrophilic macromolecules, such as proteins and FITC-dextran for a model system for parenteral drug delivery. Pistel et recite "brush-like branched polyesters, obtained by grafting poly(lactic-co-glycolic acid), PLGA, onto water-soluble poly(vinyl alcohol) (PVAL) backbones, were investigated regarding their utility for microencapsulation of proteins (e.g. abstract).

It would have been obvious to one of ordinary skill in the art to have used the polyester backbone of Pistel et al in the article of Lollo et al because Pistel et al state that their microencapsulation of hydrophilic macromolecules using a polyester backbone was a model system for parenteral drug delivery.

One of ordinary skill in the art would have been motivated to use the polyester backbone of Pistel et al in the article of Lollo et al because Pistel et al state that "grafting polyester chains onto hydrophilic backbones" yields polymers that allow manipulation of their hydrophilicity and hence compatibility with proteins in a broad range and also can control degradation and release rates (e.g. page 8, ¶ bridging left and right columns).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of polyester backbones for the purpose of micellar drug delivery was routinely practiced at the time of the teachings of Lollo et al and Pistel et al.

In view of the foregoing, the method of claims 1, 3-5, 8-16, 44 and 49-54 as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

Respectfully submitted,

Catherine Hibbert
Examiner AU1636